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Testing Times: The Emergence of the Practolol Disaster and its Challenge to British Drug Regulation in the Modern Period

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Summary. This article analyses how practolol, the first British drug disaster of the modern, post-thalidomide regulatory period, related to the pharmaceutical industry, the medical profession and government regulation of patients' health. Drawing on comparison with the USA, it argues that, contrary to public expectation and perception, the aftermath of thalidomide did not give rise to strident British drug control, imposing the highest possible safety standards on the pharmaceutical industry. Rather, there existed a culture of reluctant regulation that was characterised by continued optimism about, and trust in the purported benefits of new drugs among manufacturers and regulators in the United Kingdom, together with commitment to the protection of the industry and its institutional support for the medical profession. In particular, British regulators were willing to allow new drugs on to the market, fully aware of uncertainty about their safety, but unwilling to be pro-active in issuing warning letters about risks and requiring 'certainty' before acting to withdraw a product. Even after the practolol disaster, the British system was unable to reform itself to construct more rigorous and pro-active monitoring of drug risks. This was because of conflicts with industry interests.

Keywords: practolol; wonder drug; medicines regulation; pharmaceutical industry; drug safety; political culture

Drug disasters are among the most tragic of medical events. Nevertheless, they bring into sharp focus the commitments and workings of industry, government and related systems involved in the provision and regulation of medicines. Socio-historical analysis of such disasters can advance understanding beyond the pervasive, but superficial, view that they are an inevitable by-product of technological progress. This article focuses on the practolol disaster and how its emergence and implications related to the pharmaceutical industry, government regulation and the medical profession.

That practolol was one of the UK's worst drug catastrophes is not in doubt in human or scientific terms. By 1981, the British regulatory authorities had received approximately 2,450 reports from doctors describing adverse reactions in patients. This was more than any other medical drug in the late 1970s. Many of the reports were severe, including 40 deaths, at least 200 cases of life-threatening conditions, over 1,130 cases of eye damage, about 300 cases of deafness and over 1,250 skin reactions of varying

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seriousness.[1] However, these figures underestimate the scale of injury. The manufacturer's senior safety officer, who was in charge of the company's compensation scheme for practolol victims in the 1980s, has estimated that there were about 8,000 patients significantly injured by the drug in Britain.[2] Indeed, some former regulators, whose terms of office coincided with the licensing and/or withdrawal of the drug from the market, refer to practolol as a 'disaster'.[3]

There are several reasons for examining this series of events. First, in Britain, it was a drug catastrophe 'second only to thalidomide' and benoxaprofen in terms of scale and severity of adverse drug reactions (ADRs) relative to therapeutic advance.[4] Moreover, it has been neglected. An electronic search of the humanities and social science literature reveals dozens of articles on thalidomide, but not one on practolol. The main historical analysis to date is Vos's investigation of beta-blockers, but his research is on discovery and innovation, rather than safety and regulation.[5] More general histories of UK drug regulation by a number of researchers, for example Abraham, Lewis, Hodges and Penn, involve no analysis of practolol or the events surrounding it in the 1970s.[6] Publications by two 'insiders' in the British regulatory system offer minimal material. Mann provides two paragraphs and Inman a few valuable, but far from comprehensive, pages.[7] Histories of drug regulation outside the UK make no mention of practolol, except for Daemmrich's two paragraphs on how the government managed the drug in Germany where it also caused injury.[8]

Secondly, practolol was promoted by its manufacturer as a uniquely effective, breakthrough drug when it came on to the British market.[9] This had consequences for how it was received by the medical profession, the media and regulatory agencies. Many British newspapers, such as the *Guardian*, *Observer* and *Daily Mail* referred to practolol as a 'wonder drug'. However, histories of 'wonder drugs', such as those of penicillin by Bud, cortisone by Cantor, and interferon by Pieters, do not make any reference to the roles or performance of regulators in this context.[10] This case-study aims to fill that gap.

Thirdly, and partly because of its neglect, practolol is poorly understood. The history of the drug has been left to politicians, government regulators and industry representatives who have erected a conventional wisdom that the disaster was impossible to predict. This is within a context in which, from the point of view of understanding regulatory change in the UK, practolol is much more important than thalidomide

[1] *Hansard* 1978, w.col. 231–2; *Hansard* 1981, w.col. 124.
[2] Interview with former Head of Safety (practolol) at Imperial Chemical Industries Ltd. (hereafter ICI), 31 August 2000.
[3] Mann 1984, p. 658; Inman 1999, p. 93.
[4] Interview with expert scientist, who was a senior UK regulator during the 1970s, Southern England, 19 July 2001. The emerging drug injuries from Vioxx may turn out to make it another drug disaster with which to contend.
[5] Vos 1991.
[6] Abraham 1995; Abraham and Lewis 2000; Hodges 1987; Penn 1982.
[7] Mann 1984, p. 658; Inman 1999, pp. 93–8.
[8] Daemmrich 2004, pp. 73–4.
[9] ICI 1977.
[10] Bud 1998; Cantor 1992; Pieters 2004.

because it was the first drug disaster after the modern regulatory system of the Medicine Act of 1968 had been established. Hence, practolol presented a unique test for the new British regime.

We argue that the practolol disaster occurred in a particular social context and associated political culture, which influenced interpretative frameworks and knowledge and decision making among interested parties and agencies. The aftermath of thalidomide saw reluctant regulation *de facto*, if not *de jure*, which was ill equipped to prevent another drug disaster. Such regulation, we suggest, was committed to the protection of the pharmaceutical industry and its institutional support for the medical profession. This undermined its capacity for a sustained and pro-active critical scrutiny of new risks and benefits. It failed to give clear priority to patient safety, when such scrutiny threatened the viability of a product, the therapeutic importance of which was highly acclaimed by manufacturers and their allies in the medical profession.

Hope and Glory: Institutional Commitment to Industry and 'Breakthroughs'

During the 1960s, Imperial Chemical Industries (ICI) developed a number of drugs, known as beta-blockers, for the treatment of high blood pressure, angina and heart problems. The first of these, pronethalol, was marketed in the UK in 1962, but withdrawn within a year because it was found to be highly carcinogenic in mice.[11] However, the second, propranolol, first marketed in 1964, became a leading treatment for the next 30 years.[12] The success of propranolol was not obvious at the time. In the mid-1960s it was perceived by the medical community to be an aggressive drug and faced competition from Ciba-Geigy's oxprenolol, which was claimed to be milder and more cardio-protective. Confronted with a situation in which the general practitioner might prefer to prescribe Ciba-Geigy's alternative, ICI's marketing department decided that it would be better for the company to advance the development of a new compound to counter this competition, rather than merely to defend propranolol.

Consequently, ICI looked for a milder drug that might have some advantages over oxprenolol and propranolol. They discovered that practolol, which had first been synthesised in July 1964, produced less effect on peripheral vascular beta-receptors and bronchial beta-receptors in animal studies, but still protected the heart against excessive nervous stimulation.[13] Thus was born practolol and ICI's claims that it was a 'unique drug', particularly suitable for asthmatics who had heart problems, because it was 'cardio-selective'.[14] Company scientists also claimed that practolol was superior to other beta-blockers on the grounds that it produced fewer unwanted cardiovascular effects.[15] Dr John Waycott, director of the ICI Medical Department, described it as 'a major breakthrough'.[16]

[11] Alcock and Bond 1964; General Accounting Office 1973.
[12] Inman 1999, pp. 93–4.
[13] Vos 1991, pp. 72, 102–3, 121.
[14] Fitzgerald 1972.
[15] Wiseman 1972, pp. 20–8.
[16] Waycott 1977.

This was not the first occasion on which ICI had sought to identify itself with a 'breakthrough' drug. The company's claims about practolol must have seemed all the more powerful because of its close association with the development of penicillin. During the first half of the twentieth century, ICI was one of Britain's largest manufacturing companies and employers. As Bud demonstrates, during the 1940s the company ran an extensive publicity campaign crafting its image as a national asset through association with technological progress, and penicillin in particular.[17] However, it was widely acknowledged that practolol was no more effective, and perhaps slightly less effective, than propranolol in treating angina pectoris—chest pain from heart problems.[18] As Pentecost, George and Nagle put it:

> When an attempt is made to compare the degree of improvement achieved with practolol by similar trials using propranolol, it is found that the number of patients in whom there has been overall improvement is fewer than with propranolol.[19]

Practolol's purported safety advantages were the basis for its status as a 'wonder drug', but these may have been exaggerated. In the early 1970s, independent research began to urge caution in relation to the drug for asthmatics because it induced broncho-spasm in patients: animal studies provided no clear evidence that the drug had particular advantages or disadvantages for this group.[20] Complications, such as aggravation of heart failure or severe hypotension, were also found with use of the drug in some patients, with both reactions requiring 'energetic' medical intervention.[21] Some years later, a survey of hospitalised patients found that 'practolol and propranolol produced adverse cardiovascular effects with nearly equal frequency'.[22]

Meanwhile, in 1964, in the aftermath of thalidomide, and after consultation with the Association of the British Pharmaceutical Industry (ABPI), the British government took a first step in assessing drug safety by establishing the expert advisory Committee on Safety of Drugs (CSD), which reviewed manufacturers' testing before clinical trials and marketing.[23] Earlier, medicinal products—'ethical' pharmaceuticals—in the UK were governed by the Sale of Food and Drugs Act, 1875, which enabled regulation of adulteration, and hence drug quality, but not safety or efficacy.[24] In establishing the CSD in 1964, government advisers selected the committee members, who could not be direct employees of pharmaceutical companies, but were permitted to hold shares, consultancies and other interests in the industry.[25] The CSD had no legal powers; it depended on the voluntary cooperation of pharmaceutical firms, although all member companies of the ABPI undertook not to market any new drug in the UK against the advice of the committee.[26]

[17] Bud 1998, pp. 323–7.
[18] Robinson 1971; Areskog 1971.
[19] Pentecost *et* al. 1971.
[20] Bernecker and Roetscher 1970; Chang 1971.
[21] Claessens *et al*. 1972.
[22] Pfeifer *et al*. 1977.
[23] Anon. 1963*a*.
[24] Stieb 1966.
[25] Anon. 1963*b*.
[26] Anon. 1963*c*.

Welcoming the CSD's first annual report in 1965, the Minister of Health articulated its intended principles in the following terms:

> The Committee has emphasised that there is no way of ensuring absolute safety of drugs. By its activities, however, it ensures that new drugs introduced in the UK are as safe for their purpose as modern medical and scientific knowledge can determine, and endeavours to secure that any hazards of drugs in use are discovered as soon as possible.[27]

At the same time, the CSD expressed concern for the well-being of pharmaceutical companies. According to its chair, Sir Derrick Dunlop, the approach of the committee was that regulatory checks should not impose unnecessary restraints on the industry or interfere too much with its workings because that could be disadvantageous to major innovating companies, on whose success the medical profession depended.[28]

According to ICI, the long-term safety of practolol had been established in 127 patients, who had been treated orally with the drug for between four and 18 months. After reviewing ICI's animal toxicity tests and clinical trials, the CSD agreed, on 26 June 1970, to the marketing in the UK of practolol, under the brand name 'Eraldin', for the management of angina pectoris and cardiac dysrhythmias—or disordered heart beat.[29] Furthermore, the CSD accepted ICI's claims that the drug was 'cardio-selective', which appeared on labelling for prescribing doctors.[30] Commercially, at least, the company's promotion of practolol was very successful. In 1972, 501,700 prescriptions were written for the drug in the UK, increasing to nearly 900,000 in 1974 when it became the market leader among anti-angina drugs.[31] UK sales of about £3.8 million a year meant that practolol comprised nearly a third of ICI's prescription drugs turnover.[32]

Unfit for Human Consumption: A Precautionary Paradigm

ICI 'licensed' the American company, Ayerst, to develop and market the drug in the United States. As in Britain, the American government had first legislated to regulate only drug adulteration and quality through the Pure Food and Drug Act, 1906.[33] The Bureau of Chemistry, which was the predecessor of the Food and Drug Administration (FDA), within the US Department of Agriculture, was charged with the enforcement of this act.[34] However, unlike its British counterpart, the FDA had become responsible for assessing and regulating drug companies' safety testing in the USA since the passing of the Food, Drug and Cosmetic (FDC) Act in 1938. This measure came on to the statute book in the wake of over 100 deaths caused by the prescription drug, elixir sulfanilimide.[35] After thalidomide, in 1962, the US Congress passed the Kefauver–Harris Drug

[27]ICI 1977, p. 20.
[28]Anon. 1968; Dunlop 1971, p. 20.
[29]ICI 1977, p. 11.
[30]ICI 1974.
[31]ICI 1977, p. 1.
[32]Anon. 1974.
[33]Young 1989.
[34]Liebenau 1987, pp. 79–97.
[35]Marks 1997, pp. 71–97.

Amendments to the FDC Act, which empowered the FDA to withdraw products deemed to be unsafe or ineffective, and to require manufacturers to provide 'substantial evidence' of the efficacy of their products before approval for marketing.[36] It was within this context that the FDA came to review Ayerst's applications for use of practolol in the USA.

According to Waycott at ICI, practolol was 'comprehensively and extensively tested in the laboratory'.[37] In September 1968, ICI completed an 18-month animal toxicology study, which indicated the possibility that practolol caused cancer in mice.[38] The CSD had full knowledge of this study when they agreed to UK marketing of practolol: the results were submitted to the Committee in January 1970.[39] However, Ayerst did not submit the results of this study to the FDA until 8 April 1970, more than 19 months after completion.[40] Ayerst and ICI argued that practolol was not a carcinogen because it was not related to any known carcinogen and there was no significant statistical difference between the incidence of sarcomas—malignant growths—in practolol-treated mice and controls.[41] ICI were not concerned about practolol's possible carcinogenicity and made no mention of it on the label, and this was accepted by the CSD.[42] By contrast, FDA scientists concluded that practolol presented a carcinogenic risk to patients.[43] Analysis by an FDA pharmacologist in March 1971 indicated that there were nearly three times as many sarcomas in practolol-treated mice as controls—'a questionable (highly suspicious) increase in incidence of tumours in practolol-treated mice'.[44] In addition, FDA scientists were concerned that other beta-blockers, which were close chemical relatives of practolol, such as pronethalol, alprenolol and another ICI drug, ICI 42464, exhibited similar carcinogenic potential in rodents.[45]

Indeed, FDA's concerns about the carcinogenicity of beta-blockers led them to enrol Umberto Saffioti, Associate Scientific Director for Carcinogenesis at the US National Cancer Institute (NCI), to advise on the state of scientific knowledge on carcinogenic risk assessment. According to Saffioti:

> Proof that a substance, which has been recognised as carcinogenic in animals, actually causes cancer in man would require in most cases extremely complex and lengthy epidemiologic studies. Therefore, the only prudent course of action at the present state of our knowledge is to assume that chemicals which are carcinogenic in animals could also be such in man, although the direct demonstration in man is lacking.[46]

[36]Temin 1980, p. 123; Daemmrich 2004, pp. 24–30.
[37]Waycott 1977.
[38]General Accounting Office 1973.
[39]ICI 1977, pp. 12–13.
[40]General Accounting Office 1973, pp. 34–5.
[41]General Accounting Office 1973, p. 21; ICI 1977, pp. 12–13.
[42]ICI 1974. In a public interview in 1983, the senior medical adviser at ICI stated that they were not worried about the results of carcinogenicity tests with mice.
[43]General Accounting Office 1973, p. 22.
[44]Food and Drug Administration 1971, p. 2.
[45]Anon. 1977a.
[46]Statement of Umberto Saffiotti before the Subcommittee on Executive Reorganisation and Government Research of the Senate Committee on Government Operations, 7 April 1971, p. 2.

It may be noted that his assessment of the state of knowledge in the field was not merely based on American experience. On the contrary, Saffiotti was echoing scientific principles established internationally by the World Health Organisation in 1969, before practolol was given the 'green light' by the CSD.[47]

On the question of beta-blockers, Saffiotti told the FDA that 'in the case of drugs, when there is a carcinogenic effect in animal tests, we have to assume that there is a risk for man'. But he also stressed the need to balance such risks against benefits.[48] This should be seen in the context of a wider precautionary approach to regulatory standards for potential environmental carcinogens in the USA at that time, and more particularly of the influence of the NCI's crusade against cancer. By contrast, the British context was one in which regulators were sceptical about the extrapolative validity of animal tests to humans. At the same time, expert toxicology advisers in the CSD and other committees maintained close links with the chemical and pharmaceutical industries.[49]

Thus it was that FDA scientists began to develop more stringent pre-clinical regulatory policies towards carcinogenic risk of 'me-too' drugs compared with drugs promising significant therapeutic advance. They noted that some beta-blockers were 'me-too's' and questioned whether practolol had any therapeutic advantages over other beta-blockers.[50] Significantly, ICI's claims that the drug constituted a breakthrough were treated with considerable scepticism by the FDA, and this influenced the agency's approach to the drug's potential risks.

The FDA took the view that practolol was not even safe enough to be used in clinical trials, let alone to be marketed. As early as March 1970, the FDA asked Ayerst to stop clinical tests with the drug because of the inadequacy of other animal tests and reiterated this request a month later after receiving the results of the carcinogenicity test in mice. However, it was not until August 1971, seventeen months after the FDA's initial request, and after the FDA threatened to force the issue, that the company discontinued all clinical tests, by which time 194 patients in the USA had taken the drug in trials.[51] By 1983 the issue of practolol's carcinogenicity had still not been resolved and no results of patient follow-up for the 194 Americans had been either received or conducted by the FDA.[52]

Deconstructing the Inevitability and Unpredictability of Drug Injury

In Britain, the Medicines Act of 1968 was not implemented until 1971: this was to allow time for consultation with the industry, and for pharmaceutical companies to adjust to the legislation. The act established the Medicines Division of the Department of Health, together with the Minister of Health, as the UK Licensing Authority for new drugs. It also created the Medicines Commission to oversee and advise on the workings of the act and the Committee on Safety of Medicines (CSM) as the CSD' successor.

[47]World Health Organisation 1969.
[48]Food and Drug Administration (hereafter FDA) 1971, p. 5.
[49]Gillespie *et al*. 1979.
[50]FDA 1971, pp. 6, 9.
[51]General Accounting Office 1973, pp. 21–2.
[52]Crout 1983.

The Licensing Authority acquired legal responsibility for the regulation of drug quality, safety and efficacy, including powers, sanctioned by the state, to approve or withdraw products from the market. The highly influential role of the CSM was to provide expert advice to the Licensing Authority. But its members, like those of the CSD, were not employees of the government and were permitted to retain consultancies, fees and shares with pharmaceutical companies.[53] While the legal status of British regulation was permanently changed by the act, the personnel of the new commission and CSM were very similar to those of the CSD. Indeed, their approach was thought to be so similar that a former chief government pharmacist felt able to predict that manufacturers would hardly notice the difference when the Commission and CSM took over from the CSD.[54] Thus, the fact that practolol was first approved for marketing by the CSD just before the implementation of the Medicines Act, rather than by the CSM, is probably of little consequence.

As part of this new system, doctors were asked to report to the CSM cases when they suspected that their patients had experienced an adverse drug reaction (ADR)—the 'yellow card system'—and manufacturers were required to do the same.[55] While practolol enjoyed great commercial success in Britain in the early 1970s, reports to the CSM and in the medical literature were made about patients experiencing adverse reactions. This would later be recognised as practolol-induced oculomucocutaneous syndrome, and characterised by ICI's Head of Safety at the time as 'really horrific'.[56] The syndrome involved one or more of three components: the development of serious psoriasis-like skin eruptions; toxicity and damage to the eye, including dryness, profound vision impairment and blindness; and potentially fatal sclerosing of the serous membrane around the abdomen, lungs and–or heart, including sclerosing peritonitis. The latter caused abdominal pain, vomiting, severe constipation, pleurisy and sometimes death. As a consequence, the oral form of the drug was withdrawn from the UK market in July 1975. It could, however, continue to be used on a short-term basis in hospitals. By 30 November 1978, the CSM had received 2,184 reports of adverse reactions to practolol, including 1,130 reports of eye damage, 1,256 of skin reactions, 309 of deafness, 197 of sclerosing peritonitis (abdominal serous membrane) and 589 other manifestations of drug-induced disease.[57] Moreover, 40 practolol deaths had been reported to the CSM by February 1981.[58] The number of patients actually affected was probably far higher, as it is widely acknowledged that less than 10 per cent of ADRs are usually reported to the regulatory authorities.[59] The analyses of some commentators suggest the figure might be as low as 1 per cent.[60]

[53] Abraham 2002. For example, Dunlop moved from chair of the CSD to chair of the Medicines Commission in 1969.

[54] Anon. 1970.

[55] The voluntary reporting arrangement involving doctors became known as the yellow card system because they completed a yellow card about the ADR when making a report.

[56] Interview with former Head of Safety (practolol) at ICI, 31 August 2000.

[57] *Hansard* 1978, w.col., 231–2.

[58] *Hansard* 1981, w.col., 124.

[59] Walker and Lumley 1987.

[60] Lumley *et al*. 1986; Millar 2001; Medawar and Hardon 2004, p. 154.

ICI took the view that practolol's major post-marketing adverse effects were unique and could not have been predicted from the pre-market testing.[61] Even after the tragic post-marketing experiences, they claimed that 'no test could be devised to detect it [oculomucocutaneous syndrome] in advance'.[62] This perspective was echoed by the Department of Health when Alfred Morris, the Under-Secretary of State for Health, told Parliament that pre-market tests 'did not predict' the adverse effects of practolol, because they were 'infrequent and unexpected. Despite extensive studies with a drug in animal experiments or in clinical trials in patients, there will be occasions when adverse reactions to a drug become apparent only after widespread clinical use'.[63] Thus developed the conventional wisdom, still promulgated in the 1980s and right up to the present, that practolol was an example of how pre-market clinical testing could not detect post-marketing ADRs.[64] So widespread was this view that a popular BBC flagship television documentary introduced an investigation of practolol by stating that, 'it had totally unpredictable side effects that only emerged after it had passed all regulation safety tests'.[65] However, the evidence suggests that these claims were exaggerated and implausible.

According to Professor Bill Inman, a Principal Medical Officer in the Medicines Division of the Department of Health, ADRs characteristic of the practolol syndrome, such as dry eyes and psoriasis-like rashes, had occurred during clinical trials but their significance had not been appreciated:

> It soon became clear that the system for scrutinising drugs before marketing had also failed. We discovered that similar events had been observed during the clinical trials before marketing but had not been picked up during the process of submission or vetting of the licensing applications. Nobody had considered the possibility that late-developing peritoneal damage might have been an adverse reaction to Eraldin.[66]

Hence manifestations of the syndrome were present in the clinical testing data. Thus this process was theoretically capable of detecting the problem. However, Inman argues that in practice the rash was thought to be ordinary psoriasis. Dry eyes were dismissed as a common condition; sclerosing peritonitis was such a rare complaint that investigators and government scientists were blinded to its association with the drug.

While these assertions may be correct, they imply an interpretative framework for clinical test data that failed to make links between the new drug and adverse effects.[67] The implication was that, if a condition experienced during practolol trials was common, then it was not attributed to the drug. And if rare, it was *also* not attributed to the drug. It may be noted that if rashes and dry eyes were dismissed as common

[61] ICI 1977, p. 23.
[62] ICI 1977, p. 35.
[63] *Hansard* 1976, w. col., 2380–1.
[64] McLean 1989, p. 81; Mann 1984, p. 658.
[65] Dimbleby 1977.
[66] Inman 1999, p. 96.
[67] Secrecy laws and policies surrounding UK medicines regulation means that documentary verification of the reasoning behind government scientists' pre-market assessments of practolol is impossible.

conditions not associated with the drug, then it could not be the case, as the Under-Secretary of Health claimed, that pre-market tests failed because practolol's adverse effects were 'infrequent and unexpected'.

Furthermore, the method of collecting and recording data in the clinical trials was flawed, even though similar procedures were commonly accepted in industry, and among British regulators at the time. This was demonstrated by the epidemiologists, Professor Richard Doll and Dr David Skegg, who, after analysing the general practitioner case-notes of 71 patients before and after they received practolol, found that eye complaints were recorded in 14 cases (20 per cent) during treatment compared with four (6 per cent) during similar periods before treatment. In addition, half the patients with eye complaints also had a rash while receiving practolol, an incidence of 10 per cent.[68] By contrast, ICI scientists reported an incidence of rash in less than 0.8 per cent of patients who received practolol orally during clinical trials, and no eye complaints at all.[69]

According to Skegg and Doll, this high incidence of eye conditions in such a small study suggested that practolol's ocular toxicity could have been detected in pre-market clinical trials. That it was not, in their view, was not due to deliberate concealment, but because clinical investigators recorded only suspected ADRs, rather than all adverse experiences of patients taking the drug and placebo during the trials, together with an analysis of the latter data to help to determine which experiences were, in fact, drug-related. Recording and reporting only those conditions which the clinical investigator initially suspected were ADRs was likely to under-state the toxicity of practolol because 'it is extremely difficult to decide whether the drug is responsible, and when doctors are enthusiastic about a new treatment they may be reluctant to blame the drug'.[70] They concluded that, had regulators and physicians been alerted to these 'relatively common effects of practolol' through pre-market clinical trials, this would have led to earlier diagnosis and withdrawal of the drug from patients who developed severe conditions, including blindness.[71] Thus the practolol disaster was, in part, the result of inadequate clinical trial techniques and regulatory review of these trials. It was not predicted, but it was not an inevitable consequence of the unpredictability of introducing new drugs on to the market. On the contrary, the practolol affair is an example of how clinical trials could have detected important toxicities if interpretations of patients' adverse experiences had been more critical of the drug, thus allowing the collection of more complete data sets.

Experts, Uncertainty and the Social Commitments of Caution

In the aftermath of thalidomide, the yellow card system was established as an early warning mechanism to help to prevent drug disasters by sending a signal of a drug's dangers to regulators *after* the drug had come on to the market. Since not all ADRs can be detected by pre-market testing, the yellow card system was supposed to provide an additional safety net by detecting uncommon and unusual ADRs that might

[68]Skegg and Doll 1977*a*.
[69]Wiseman 1971.
[70]Skegg and Doll 1977*b*.
[71]Skegg and Doll 1977*a*, p. 477.

not be identified before marketing because, as Professor Eric Scowen, chair of the CSM at the time explained, clinical trials are too small to detect some ADRs.[72]

Autumn 1972 saw prescribing doctors report to ICI and the CSM some rather serious skin reactions caused by practolol and first identified about a year after the drug went on the market.[73] The first reported case of the auto-immune disorder, systemic lupus erythmatosis (SLE), occurred in August 1971.[74] There was a case of the potentially fatal exfoliative dermatitis, involving intense generalised itching, psoriasis-like rash, peeling of the skin and ulceration of the face.[75] Indeed, on 23 May 1972, a heart specialist reported that tests in his clinic resulted in 10 per cent of patients on practolol developing chronic skin rashes—usually psoriasis-like—which disappeared on stopping the drug.[76]

Neither ICI nor the CSM took any action. The company felt that the rashes were not 'a serious warning'.[77] The CSM believed the skin reactions were 'disturbing, but not disastrous, compared with the effects of practolol'.[78] The commitment to practolol as a 'breakthrough' drug dissuaded the CSM from requiring even a change in the label to provide early warning of these risks. By January 1974, there had been 21 cases of practolol-induced SLE. As a consequence, ICI changed the label to read, 'very rarely a drug-induced SLE-like syndrome, reversible on stopping treatment, sometimes characterised by skin rashes with fever and joint pains, has been reported; in these patients, treatment should be discontinued'.[79] There was no mention of 10 per cent of patients in one clinic suffering practolol-induced skin reactions. On 8 June 1974, Dr Peter Wright published cases of practolol-induced, psoriasis-like skin eruptions combined with ocular toxicity, such as dryness of the eyes and conjunctival shrinkage and scarring—cases which he had first come across as early as autumn 1973.[80] In response, ICI sent a letter to doctors and pharmacists on 12 July 1974 warning them of the skin and ocular toxicity associated with practolol and advised them to discontinue the drug in any patients exhibiting skin or ocular symptoms.[81] Despite the fact that practolol was no more effective than propranolol and other beta-blockers at the time, ICI did not send a warning that practolol should only be used in patients who failed to respond to equally effective drugs. Despite its authority and standing with the medical profession, the CSM did not issue a warning. According to Scowen, this was because the evidence they possessed was 'negligible'.[82] However, according to ICI, the first warning was drawn up in consultation with the CSM after the latter had discussed Wright's cases on 10 July 1974. Clearly, then, the CSM could have

[72] Scowen 1977.
[73] These links are said to be causal because the reaction stopped and re-started when the drug was terminated and re-administered, respectively, or stopped when the drug was withdrawn.
[74] *Observer* 1976; Raftery and Denman 1973.
[75] Rowland and Stevenson 1972.
[76] Zacharias 1972; BBC *Panorama*, 23 May 1972.
[77] Waycott 1977, BBC *Panorama*.
[78] Scowen 1977, BBC *Panorama*.
[79] ICI 1977, p. 22; Felix and Ive 1974; Interview with former Head of Safety (practolol) at ICI, 31 August 2000; ICI 1974.
[80] Wright 1974, 1975.
[81] ICI Pharmaceuticals Division 1974.
[82] BBC *Panorama*.

demanded all the details held by ICI in order to issue their own warning. A senior regulator at the time recounted that other considerations proved influential:

> I think that the Committee felt that it shouldn't become associated with heavy-handed, big brother sort of actions. . . . It was felt in some cases if the watchdog Committee made a statement, that would virtually wipe the drug off the market because doctors would be too frightened of litigation to try the drug, whereas the company would say, be careful chaps, there are these precautions.[83]

This suggests that the CSM's generally sympathetic view of the industry's desire for minimal regulation was reflected in their handling of the practolol case, and that the Committee's commitment to the benefits of keeping ICI's product on the market outweighed its commitment to proactive use of its own early warning system.

The first ICI warning precipitated a flood of reports to the CSM, including nearly 100 descriptions of eye damage, from dryness to corneal ulceration and blindness.[84] Meanwhile, in August 1973, the first patient with practolol-induced sclerosing peritonitis underwent surgery, followed by a second in May 1974, and a third in September 1974.[85] On 9 October 1974, ICI sent a second warning letter about practolol's adverse effects to doctors and pharmacists reporting 93 patients with eye damage, 71 skin reactions and four cases of sclerosing peritonitis. The company stated that it was working with the CSM to determine the 'extent of reversibility' of the ocular toxicity and described the 'causal relationship' between practolol and sclerosing peritonitis as 'unclear'.[86] However, two months later, doctors published these three cases of sclerosing peritonitis, establishing causality with practolol: 'Other possible causes of this sclerosing peritonitis can be excluded, and the possible involvement of practolol in these cases is supported by identification via the CSM of four similar cases'.[87]

Moreover, for one of these patients, the sclerosing peritonitis progressed *after* treatment when practolol had stopped, suggesting that in some cases the disease was not reversible. On 31 December 1974 another patient, who had stopped taking the drug eight months earlier, underwent surgery for practolol-induced sclerosing peritonitis, indicating to the reporting doctors that once initiated, peritonitis was 'a continuing process', irrespective of withdrawal of practolol.[88] Many more reports of practolol-induced sclerosing peritonitis were now published.[89] In January 1975, the CSM made its first intervention in relation to practolol by circulating a leaflet warning doctors and pharmacists that in some cases its association with ocular damage 'may be irreversible'.[90] This realisation did not move the CSM or the manufacturer to withdraw the drug from the market. It was not until 18 April 1975 when ICI

[83]Interview with senior UK regulator during 1970s, southern England, 19 July 2001.
[84]Inman 1999, p. 95.
[85]Eltringham *et al*. 1977.
[86]ICI Pharmaceuticals Division 1974.
[87]Brown *et al*. 1974.
[88]Dunstone and Ive 1975.
[89]For example, Meyboom 1975.
[90]Committee on Safety of Medicines (hereafter CSM) 1975.

sent its third warning letter that any fundamental restrictions on the use of the drug were recommended:

> The incidence of reactions affecting the eyes and more particularly the severity of the peritoneal lesions have proved to be such that we now recommend that Eraldin should be reserved for the treatment of patients where it has specific benefit compared with alternative treatment.[91]

On 10 May 1975, Halley and Goodman published a further three cases of practolol-induced sclerosing peritonitis which had progressed for months after treatment had stopped.[92] According to ICI, this publication 'made it clear that the reaction could be experienced long after the drug was withdrawn, and that withdrawal of the drug on the onset of a rash did not, as had been believed, avoid the development of any more serious disorders'.[93] The company then sent a final letter to doctors and pharmacists on 30 July 1975 stating that, because of practolol's adverse effects, the drug would be withdrawn from general use on 1 October 1975.[94] However, as Halley and Goodman noted, there had been other published cases of onset and progression of sclerosing peritonitis after discontinuation. One had been as early as December 1974, the others in January and March 1975.[95]

When asked why the CSM had not acted earlier to withdraw practolol from the market, Scowen replied that the Committee had 'two problems: to be certain of the facts and to avoid unnecessary panic'. Patients who needed practolol might suddenly be denied access to it.[96] Similarly, the ICI Medical Director took the view that 'a comparatively small number had been harmed' by practolol, relative to 'the enormous benefits' of the drug.[97] Under conditions of uncertainty, the CSM adopted a highly sceptical view, and was cautious about accepting the dangers of practolol. Greater certainty could only be gained by the emergence of more cases of irreversible severe harm. Thus the CSM demanded compelling evidence of very serious, life-threatening and sometimes irreversible injury before it would withdraw a drug. This may be contrasted with the committed acceptance of the company's claims about practolol's therapeutic benefits compared with other beta-blockers, which were also subjected to critical scrutiny by the FDA.

In addition, both the CSM and ICI implied that withdrawing the drug from the market earlier would have militated against benefit to patients. Yet practolol was no more effective than propranolol, its supposed safety advantages for asthmatics were already being contested, and ICI had recommended that patients could be confidently switched to propranolol in its warning letter on 18 April 1975. Thus:

> For most patients in whom beta blockade is indicated we would recommend the use of propranolol—our original beta-blocking drug which has been in clinical use for ten years [and] can be prescribed with confidence.[98]

[91] ICI Pharmaceuticals Division 1975*a*.
[92] Halley and Goodman 1975.
[93] ICI 1977, pp. 28–9.
[94] ICI Pharmaceuticals Division 1975*b*.
[95] Brown *et al*. 1974; Dunstone and Ive 1975; Bendtzen and Soborg 1975; Kristensen *et al*. 1975.
[96] BBC *Panorama*.
[97] Waycott 1977, BBC *Panorama*.
[98] ICI Pharmaceuticals Division 1975*a*.

Post-disaster Capacity for Regulatory Change

In the aftermath of the practolol disaster, the British government did not accept that the drug's tragic effects could have been identified through better pre-market clinical testing or that the Licensing Authority and the CSM should have acted on signals of injury earlier to issue restrictions and–or withdraw the drug from the market. However, it did accept that the yellow card system had major limitations in early detection of previously unknown ADRs. In this context, Alfred Morris, the Under-Secretary of State for Health, set the agenda for improving post-market drug regulation as follows:

> if we can devise systems which would lead to earlier detection of unexpected adverse reactions, at least something positive may have come out of the many individual tragedies which have resulted from the use of Eraldin.[99]

In response, in 1976 the CSM established a working party to consider ways of supplementing the yellow card system.[100] Although no minutes from the meetings of this working party are publicly available, it is clear that the committee considered published proposals for reform, some of which came from the CSM's own secretariat and from conferences involving members of the CSM.[101] For example, W. H. W. Inman, among others, outlined a system of 'recorded release' for new drugs whereby selected products would be approved on a provisional basis.[102] This would involve doctors sending a form to the CSM containing a copy of the first prescription written for a patient and basic clinical information. Suspected ADRs would be reported via a yellow card in the normal way, but in addition and at certain time intervals, doctors participating in the scheme would be asked to return a second form recording any illnesses or health concerns reported by the patient and details of any referrals or hospital admissions. The scheme would also allow the CSM to monitor the possibility of late-onset effects with drugs under surveillance. Similarly, Dollery and Rawlins proposed a scheme of 'registered release' which would require pharmaceutical companies to complete a quota of five to ten thousand patient registrations for a new drug *before* it went on widespread sale.[103] Registered patients would then be followed up in the manner proposed by Inman. This would have formally slowed the release of new drugs on to the market, but also provided more time and evidence for assessment of ADRs before marketing to a potentially huge patient population. Dollery and Rawlins also suggested that information could be obtained from registered patients who would be asked to fill in a questionnaire.

Noting these proposals, the chair of the CSM sought consultation with interested parties, including the pharmaceutical industry.[104] Significantly, the ABPI made it publicly known that it was opposed to a scheme of restricted release for new drugs because it would 'unnecessarily inhibit the freedom of doctors to prescribe a new medicine'.[105] However, an article in the industry journal, *Scrip*, suggested that an important reason

[99] *Hansard*, 1976, w. col. 2383.
[100] Anon. 1976*a*.
[101] Anon. 1977*b*.
[102] Inman 1977.
[103] Dollery and Rawlins 1977.
[104] Scowen 1977.
[105] Wilson 1977.

for industry opposition was that such a scheme would have inevitably reduced sales in the initial period of new marketing.[106] Moreover, this debate took place in the context of a major balance of payments problems for the British government following the oil price explosion in 1973. Since the end of the Second World War, the pharmaceutical industry's highly successful export trade had made a significant contribution to the balance of payments. The ABPI were well aware of this and were only too ready to emphasise it within the context of drug regulation:

> The contribution of the industry should be taken as a whole—its help in reducing problems of the Chancellor of the Exchequer by maintaining the value of sterling abroad should be put alongside its ability to deliver the goods for our own Health Service.[107]

When the British Chancellor of the Exchequer found himself forced to obtain a £3.9 billion loan from the IMF in 1976 on conditions of reductions in public expenditure and the adoption of proto-monetarist policies, the government switched its priorities to those set by industry, rather than regulatory intervention by the state.[108] As premier James Callaghan stated in November of that year:

> We must give absolute priority to industrial needs ahead of even our social objectives. . . . We must ensure that industry is profitable and aim for faster growth and high productivity.[109]

The National Economic Development Council's 'sector working party' on the pharmaceutical industry concluded in 1976 that, in order for it to maximise its contribution to a positive balance of payments through expansion of direct export and import substitution, the Department of Health should seek to minimise interference with the industry.[110] As the President of the ABPI explained, 'no company can afford to expend more on preliminary testing than it can expect to recover in sales'.[111] For its part, the industry pressed for reductions in pre-market testing requirements and resisted curtailment of its sales by measures such as recorded, registered and monitored release of new products. The CSM was asked to look at ways of helping the industry with these objectives in mind.[112]

Nevertheless, the CSM was initially prepared to restrict the number of patients who could be exposed to a new drug during the post-approval phase.[113] Indeed, a consultation letter outlining such a scheme for all new drugs was sent out to the ABPI, the Pharmaceutical Society of Great Britain and the British Medical Association in 1978.[114] But by the end of 1978, the CSM had abandoned its plans for a scheme of recorded release of new medicines as being 'not practicable'.[115] Several members of the CSM

[106] Anon. 1976*b*.
[107] Anon. 1959.
[108] Thompson 1984, p. 286.
[109] Association of the British Pharmaceutical Industry (hereafter ABPI) 1977, p. 9.
[110] Anon. 1976*c*.
[111] Smart 1981.
[112] Anon. 1976*d*.
[113] Anon. 1977*c*.
[114] Anon. 1978*a*.
[115] Anon. 1978*b*.

and senior regulators have confirmed that the CSM quickly abandoned its commitment to recorded or registered release because of politically inspired industrial opposition, and cost.[116] As a former regulator in the Department of Health put it:

> The Adverse Reactions [Sub-Committee of the CSM] was very supportive of recorded release. . . . The Committee [CSM] *liked* the idea, but they wouldn't accept it because they said it was too expensive, it was too tough on the industry. . . . [because] it would make new drugs very much more difficult to sell. . . . Senior medical administrators [in Dept of Health] didn't want it, the non-medical administrators didn't want it. . . . It was all possible, but it's just not happened. I do believe that employment and votes have got a lot to do with it, because everything that we've talked about would be potentially reducing the amount of money that drug companies would make.[117]

Consequently, the post-marketing system for monitoring new drug safety remained the same as before the practolol disaster. There were two minimal changes to pre-market regulation: completion of carcinogenicity testing before clinical trials for beta-blockers became a requirement for a few years and new drugs intended to be taken long-term by patients had to be tested in pre-market trials on about 100 patients for up to a year.[118] However, Skegg's proposal that all adverse experiences rather than suspected drug reactions of patients taking a new drug and placebo during the pre-market trials should be reported, did not become a regulatory requirement until well on into the 1980s after a further major drug disaster, that associated with benoxaprofen.[119]

Conclusion

This case study reveals a pervasive culture of great optimism about the purported benefits of new drugs among manufacturers, regulators and the medical profession in Britain. Cantor's research has demonstrated that such a culture existed during the introduction of cortisone in the early 1950s before thalidomide and drug safety and efficacy regulation in Britain.[120] That such optimism persisted after the thalidomide disaster, and beyond the introduction of such legislation, is clear from this case study. The culture of optimism was spearheaded by the pharmaceutical industry, but strongly endorsed by key regulators who were also senior members of the medical establishment. The post-thalidomide regulatory system was shaped by reluctance to interfere with the productivity of the industry because of its contribution to the macro-economy, its institutional support for the medical profession and an enormous trust in science-based innovation. The fluidity of this culture permitted expert regulators to move readily between acting as medical scientists in drug development for pharmaceutical companies, and advising government.[121] In particular, the financial and institutional links between the industry and regulators were

[116]Interviews with former members of CSM in 1970s, southern England, 19 and 28 June 2001.
[117]Interview with senior UK regulator during 1970s, southern England, 19 July 2001.
[118]Fletcher 1989.
[119]Interview with senior expert scientist, who was formerly member of CSM during 1980s, southern England, 19 June 2001.
[120]Cantor 1992.
[121]Jasanoff 1990.

often very close. All this created sympathetic conditions for the industry within the decision-making process.

Within this context, British regulators largely accepted ICI's claim that practolol constituted a 'major breakthrough', even though the drug's benefits compared with propranolol were uncertain and at best marginal. In line with this culture, adverse patient experiences during pre-market clinical trials, which would subsequently prove to be very significant, were not attributed to the drug. The commercial and institutional rewards for new products engendered an enthusiasm that encouraged clinical investigators to seek other explanations for adverse patient experiences, while scientific techniques developed by the medical-industrial complex permitted them to do so.

There are parallels here with Pieters' analysis of interferon as part of 'modern medicine's expectations trap'.[122] He argues that promotion of interferon as a 'miracle drug' in the media created inflated expectations among British patients and doctors which were dashed when the anti-cancer therapy failed to be particularly effective. Our case study generates the hypothesis that such expectations can also permeate regulatory culture, and hence, also, the risk–benefit assessment process within relevant agencies, which underpins decisions about how soon and how restrictively to act against a drug which raises major safety concerns. Moreover, regulators were willing proactively to approve new drugs and allow them on to the market, fully aware of uncertainty about their safety. Yet they were unwilling to be proactive in issuing warning letters about practolol, and they required 'certainty' before *withdrawing* the drug. In addition, international comparative evidence from the USA indicates that a very different approach was possible—one which interrogated claims about practolol's unique benefits and set stringent standards for the demonstration of safety for patients. The British approach of requiring scientific causality of harm regarding either human ADRs or carcinogenicity status coincided with the industry's perspective and reinforced a culture of reluctant regulation.

Overall, then, the evidence suggests that the practolol disaster is in part explained by a distinctive regulatory culture in Britain, characterised by an industry perspective emphasising benefits over risks to patients. In this respect, the system operated in quite the opposite fashion to public expectations after thalidomide.[123] The system was supposed to be independent of industry precisely because it was felt that interested pharmaceutical companies should not be allowed to withdraw their own products. Public expectation was that the regulatory culture would develop a system that was sufficiently precautionary about drug risks that it would prevent another drug disaster, although not, of course, all ADRs.

Even after a second drug disaster, and a considerable shift in the CSM's concern about the adequacy of drug safety regulation, the British system was unable to reform itself to construct more rigorous and proactive monitoring of risks to patients because it might conflict with the commercial interests of the industry. This confirms a 'corporate bias' of the regulatory culture at all levels of government, and one which prioritised the industry's commercial goals and product output over patient safety.[124]

[122] Pieters 2004, pp. 225–9.
[123] Daemmrich 2002.
[124] Abraham and Sheppard 1999.

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